

Symptomatic Carotid Stenosis

– Optimal Timing of Surgical Treatment

Sofia Strömberg



UNIVERSITY OF
GOTHENBURG

Wallenberg Laboratory,
Institute of Medicine
At Sahlgrenska Academy
University of Gothenburg

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sofia.stromberg@vgregion.se

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To whom it may concern,

Abstract

In patients with symptomatic carotid artery stenosis is convincing evidence that carotid endarterectomy (CEA) confers maximum benefit if performed within 14 days from index event. Patients with TIA or minor stroke have an increased risk of early recurrent stroke in the first weeks after the index event, then declining over months. This is the rationale to perform CEA as soon as possible after an index event. However, the procedural risk within the urgent time period is unknown.

Aim

The overall aim of this thesis was to investigate the optimal timing of surgical treatment in patients with symptomatic carotid stenosis.

Methods

In study I, registry data, obtained from Swedvasc, was analyzed regarding procedural risk of CEA, stratified for delay from index event. Mortality and stroke rate was studied at four time points, 0-2 days, 3-7 days, 8-14 days and 15-180 days. A multivariable analysis was performed to find other risk factors for CEA than time from referring event.

In study II, 397 patients from WINGA, a region based registry for ultrasound investigations, were analyzed. All included patient had a significant symptomatic carotid stenosis. The risk of recurrent stroke at day 2, 7 and 30 after the index event was analyzed.

Study III, was a prospective population based study with 418 consecutive patients comparing CEA within 48 hours with CEA after 48 hours to 14 days from most recent event. Primary endpoint was 30 days stroke and/or mortality rate after CEA.

Study IV, included all CEA for symptomatic carotid stenosis registered in Swedvasc from May, 2008 to October, 2014. All medical records for CEA performed within 2 days were collected, and also a control group with CEA 3 to 7 days from index event. Analysis of validated and crude data regarding procedural risk stratified for delay was made.

Results

The overall results from the four studies in the thesis shows an early risk of recurrent stroke at 1.7-2.0% day 2, 4% at one week and 7.5% at day 30. The procedural risk was 7.3-11.5% when CEA was performed within 2 days, 2.9-3.6% in patients with CEA 3 to 7 days, and 3.0-5.0% if surgery was performed 3 to 14 days after index event.

Conclusions

In summary, the procedural risk exceeds the risk of recurrent stroke day 0 to 2 in the studies in this thesis. The procedural risk, when 48 hours have elapsed after index event are not associated with an increased risk compared to even later surgery. This advocate a more expedited intervention than today's guidelines recommend. The exception should be day 0 and 1, where only a minority of patients benefit from surgery.

Keywords

Carotid artery stenosis, carotid endarterectomy, stroke, transient ischemic attack, ocular transient ischemic attack

Sammanfattning på svenska

Cirka 22 000 personer får stroke varje år i Sverige. Tiotusen personer dör i Sverige varje år till följd av stroke. Det är den sjukdomsgrupp som behöver flest vårdtygn. Cirka 85 % av alla stroke beror på hjärninfarkt och cirka 10 % av dem är orsakade av en förträngning i halspulsådern (karotisstenos).

Åderförfettning (ateroskleros) i halskärl är ett relativt vanligt tillstånd hos äldre människor. Åderförfettning utvecklas över tid och gör pulsådern styvare, tjockare och blodströmmen blir smalare.

Man uppskattar att 10 % av befolkningen över 80 år har karotisstenos. De flesta som har karotisstenos har inga besvär eller symtom. Ibland sker en förändring i placket som bidrar till att små fragment åker med blodflödet upp i hjärnan. Detta kan ge symtom i form av ensidig förlamning, talsvårigheter, plötslig blindhet. Antingen går symtomen över inom 24 timmar, och då kallas det transitorisk ischemisk attack, TIA, eller får man mer varaktiga symtom, stroke.

Stora randomiserade studier har visat att kirurgisk behandling av karotisstenos minskar risken för återinsjuknande i stroke jämfört med endast medicinsk behandling.

Den kirurgiska behandlingen av karotisstenos syftar till att minska risken för ny stroke. Rekommendationen är att behandla patienter med symptomgivande karotisstenos skyndsamt. Medicinsk behandling med acetylsalicylsyra och kolesterolsänkande skall startas omedelbart och utredning med ultraljud görs så snart som möjligt för att hitta de som har en förträngning på halspulsådern. Inom 14 dagar bör operation av karotisstenos äga rum, för att förhindra så många nya strokes som möjligt.

Att man skall operera inom 14 dagar är välstuderat, men däremot saknas bevis för när inom dessa 14 dagar som patienterna har mest nytta av operation. Det har också skett en utveckling de senaste åren vad gäller medicinsk behandling och risken för att återinsjukna i stroke efter ett symtom från en karotisstenos kan ha förändrats jämfört med de studier som tidigare har gjorts.

Studierna i denna avhandling avser;

Att studera risken att återinsjukna i stroke hos patienter med en symptomgivande karotisstenos med dagens medicinska behandling.

Att studera risken att drabbas av stroke eller död vid operation av karotisstenos avhängigt av när operationen äger rum i förhållande till tiden för symtom.

Studie I är en nationell populationsstudie där risken vid akut kirurgi, inom 2 dagar från neurologisk varningshändelse, visar sig vara signifikant högre än om man opereras efter dag 2.

Studie II är en populationsstudie från Västra Götalandsregionen där patienter med symptomgivande karotisstenos som har gjort ultraljudsundersökning av halskärnen studeras för att analysera risken för återinsjuknande i stroke. I denna studie är risken för ny stroke lägre än i de flesta äldre studier, vilket skulle kunna bero på en bättre medicinering.

Studie III, är en planerad populationsstudie där vi jämför risken att opereras akut inom 48 timmar från neurologisk varningshändelse med operation dag 3-14. Här fann vi en signifikant ökad risk vid akut operation jämfört med den senare behandlade gruppen.

Studie IV är en uppföljande studie av studie I som i en validerad population visar en hög risk vid akut kirurgi, dag 0 och 1, jämfört med patienter som opereras dag 2 till 7 (15.8% jmf 5.4%, OR 3.31, 95 % CI 1.47 – 7.45).

Sammanfattningsvis är tidig operation, inom 14 dagar säker med undantag för de första två dagarna. Man bör fortsatt vara försiktig med operation inom detta akuta tidsintervall men därefter finns ingen anledning att dröja ytterligare med operation. Lämpligen skulle riktlinjerna ändras för att påskynda operation. De första två dagarna bör ägnas åt den viktiga medicinska behandlingen och utredning inför kirurgi. Fler studier behövs för att ta reda på operationsrisk och risk för återinsjuknande i stroke med dagens medicinska behandling.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Strömberg S., Gelin J., Österberg T., Bergström G.M.L., Karlström L., Österberg K., for the Swedish Vascular Registry (Swedvasc) steering committee

Very urgent carotid endarterectomy confers increased procedural risk

Stroke 2012; 43:1331–1335.

- II. Strömberg S., Nordanstig A., Bentzel T., Österberg K., Bergström G.M.L.

Risk of early recurrent stroke in symptomatic carotid stenosis

European Journal of Vascular and Endovascular Surgery 2015; 49:137-144

- III. Nordanstig A., Rosengren L., Strömberg S., Österberg K., Karlsson L., Bergström G.M.L., Fekete Z., Jood K.

Very urgent carotid endarterectomy is associated with an increased procedural risk: The Carotid Alarm Study

European Journal of Vascular and Endovascular Surgery 2017; 54:278-286

- IV. Strömberg S., Bergström G.M.L., Acosta S., Gillgren P., Karlöf E., Johansson E., Klingberg D., Österberg K., for the Swedish Vascular Registry (Swedvasc) steering committee

Procedural risk of very urgent carotid endarterectomy – A population based study

Manuscript

Content

13	Abbreviations
15	Introduction
15	Background
16	History of carotid endarterectomy
17	NASCET and ECST
18	Imaging
18	Ultrasound
19	Plaque morphology and biomarkers
20	Risk Score
20	Treatment of symptomatic carotid stenosis
20	Medical treatment
22	Surgical treatment
24	Timing of carotid endarterectomy
24	Definitions in literature
25	Risk of recurrent stroke
25	Procedural risk
26	Changes over time
27	Aims
28	Patients and Methods
28	Study design
29	Swedvasc (study I and IV)
29	WINGA (study II)
30	Definitions
31	Ethical approval

31	Patients and primary endpoints
31	Study I
32	Study II
33	Study III
34	Study IV
35	Statistical methods
36	Results
36	Summarized results
36	Study I
39	Study II
40	Study III
41	Study IV
41	Validated data
41	Crude Swedvasc data
43	Discussion
43	General discussion
43	Natural history of symptomatic carotid stenosis
46	Procedural risk of CEA stratified for delay
49	Optimal timing of CEA
50	Changes over time
51	Methodological considerations and limitations
51	Selection bias
52	Confounding
52	Power
53	Conclusion
54	Future perspective
55	Acknowledgements
58	References

Abbreviations

AHA	American Heart Association
ABCD2	Scoring risk including; Age,Bloodpressure,Clinical manifestations,Duration,Diabetes
ABCD3-I	See ABCD2, Dual TIA and carotid Imaging added
BMT	Best Medical Treatment
CAR	Carotid Artery Risk score
CCA	Common Carotid Artery
CEA	Carotid EndArterectomy
CI	Confidence Interval
DAPT	Dual AntiPlatelet Therapy
ECA	External Carotid Artery
ECST	European Carotid Surgery Trial
ICA	Internal Carotid Artery
MRI	Magnetic Resonance Imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institutes of Health Stroke Scale
NR	Neurological Recurrence
OMT	Optimal Medical Treatment
OR	Odds Ratio
P-value	Level of significance
Pts	Patients
RCT	Randomized Clinical Trial
SCS	Symptomatic Carotid Stenosis
SD	Standard Deviation
SIE	Stroke In Evolution
Swedvasc	SWEdish VASCular Registry
TIA	Transient Ischemic Attack
WHO	World Health Organization
WINGA	Western region INitiative to Gather information on Atherosclerosis

Introduction

Carotid stenosis as a cause of stroke

"A stroke is caused by the interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue."

(The definition of stroke by the World Health Organization.)

Stroke is one of the most common causes of disability among adults worldwide and the second most common cause of death. Over the last years the incidence of ischemic stroke has decreased in high income countries while it increases in middle and low income countries during the same time.¹ However, there is a shift in the incidence in relation to age, stroke is increasing in younger patients in high income countries.²

Background

Stroke is the comprehensive term for ischemic and hemorrhagic damage to brain tissue. In Sweden it is the most common cause of hospitalization. Nearly 22 000 patients were registered with stroke in the national stroke register, RiksStroke, in 2016 and further 10 000 patients were registered due to a transient ischemic attack (TIA).³ The etiology of stroke is in 86% ischemic and the most common cause is a cardio-embolic event. Approximately 15% of ischemic strokes are due to lesions in the extracranial or major intracranial arteries.^{4,5}

Atherosclerosis is a multifocal disease, affecting predominately large and medium-sized arteries, particularly where there is branching, tortuosity or

confluence of vessels. Angiographic, pathological and ultrasonic studies shows that the most common extracranial sites for atheroma are the aortic arch, proximal subclavian arteries, carotid bifurcation, and the vertebral artery origin. If a plaque in the carotid bifurcation ruptures it may dislodge plaque fragment, or stimulate to formation of thrombosis with subsequent embolism, most frequently into the area of distribution of the middle cerebral artery (MCA).

In a neuro-epidemiologic study from 2013 the specific extracranial internal carotid artery disease causes approximately 8% of the ischemic strokes.⁶ Population-based registries on incidence involve a number of problems, the most important being completeness of case ascertainment. Patients with mild stroke never seeking hospital and patients with fatal stroke may be missed.

History of carotid endarterectomy

In 1953, DeBakey performed the first successful thromboendarterectomy for cerebrovascular insufficiency caused by an atherosclerotic occlusion of the carotid artery. In 1975, he himself wrote a case report, a nineteen years follow up study. The patient was observed until his death from coronary occlusion 19 years after carotid endarterectomy. Throughout that time the restored circulation in the carotid arteries was maintained.⁷

During the subsequent two decades the number of these procedures grew. Fifteen thousand CEAs were performed in the United States 1971, and this increased to 34000 in 1976. With an increased number of CEAs performed, more complications with peri-operative strokes were noticed.⁸ The fear of bringing more harm than good in these patients increased among the clinicians, which eventually led to two landmark RCTs; The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and The European Carotid Surgery Trial (ECST).^{9,10}

NASCET and ECST

In ECST and NASCET almost 6000 patients in over 200 centers were randomized, comparing best medical treatment alone and best medical treatment together with CEA. The main inclusion criteria was ipsilateral carotid territory symptoms within the preceding six months. Both trials showed that CEA conferred significant benefit in symptomatic patients with a 70% to 99% stenosis. Based on these two randomized trials for symptomatic carotid disease, there is consensus that patients with TIAs, ocular TIAs, or minor stroke with good recovery and with 70% or greater carotid stenosis will benefit from surgery with an absolute stroke risk reduction of 17% at 2 years (NASCET) or approximately 10% at 3 years (ECST).

In NASCET patients with symptomatic moderate stenosis (50-69%) also will benefit from surgery. The European and North American methods to determine degree of stenosis differs and a 70% stenosis by the European method is equivalent to a 40% stenosis by the North American method. Thereby the ECST could not find any benefit for surgery for the moderate stenosis determined by the ECST-method (Fig.1).

The conclusion in both studies was that carotid endarterectomy is of proven value in stroke prevention in selected symptomatic patients. The long-term benefits are linked to initial operative risk. In selecting patients for CEA surgeons must consider both perioperative risks and life expectancy span contra stroke risk.

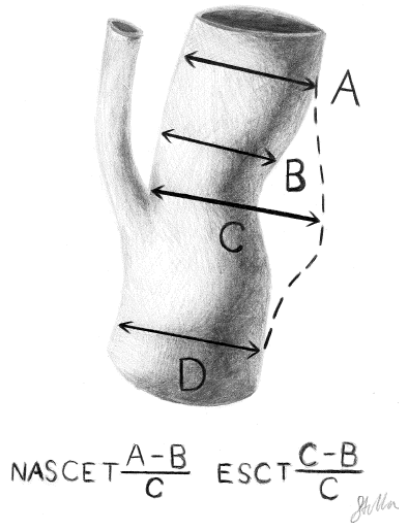


Figure 1. Two different methods for calculating degree of stenosis.

Imaging

Ultrasound

The appropriate diagnostic algorithm prior to CEA has changed over the past years. Angiography was initially considered the golden standard as preoperative investigation, and used in the NASCET and ECST studies. Today most patients are investigated with duplex ultrasound alone. The major issues that must be addressed are the accuracy of duplex in grading the severity of the stenosis.

There are several studies showing that, in expert hands, duplex scanning was equivalent to calculation of the degree of stenosis on angiography. Evidence suggests that if an experienced duplex operator perform the investigation the duplex has a sensitivity and specificity of 90% in detecting a stenosis $>70\%$.¹¹ The duplex examination gives accurate information regarding degree of stenosis, the length of the lesion and characteristics of the plaque.

Several studies have analyzed the benefit of CEA stratified for the severity of the stenosis.

In pooled data from NASCET, ECST and the Veteran Affairs (VA) studies, Rothwell et al showed the absolute risk reduction of stroke and death at five years in symptomatic patients undergoing CEA with 50-69% and 70-99% carotid stenosis. This was also dependent on time from randomization to CEA.

The benefit conferred by surgery diminished rapidly as the interval between randomization and CEA increased, especially in patients with 50-69% stenosis (NASCET).¹²

Plaque morphology and biomarkers

The vulnerability of the plaque has been the subject of many studies in order to find patients at high risk for recurrent stroke. A study based on data from ECST showed that angiographic plaque surface irregularity is associated with an increased risk of ipsilateral ischemic stroke.¹³

This factor is therefore included in the CAR-risk score, which is derived from the ECST. Furthermore, an ulceration or intra-plaque hemorrhage is associated with an increased risk of recurrent stroke, but no other characteristics of the plaque have been identified to correlate to elevated risk.¹⁴

Ultrasound is the first-line modality for carotid disease and identifications of plaque ulcerations, but MRI with high resolution is also valuable for evaluating plaque composition.

There are several studies that analyze different biomarkers that may be associated with vulnerability of the plaque.¹⁵ None are validated to be used in every day clinical practice.

Risk Score

In the last decade, scores have been established to estimate the stroke risk following a TIA. The ABCD2 and the ABCD3-I scores are regarded as the best validated ones.¹⁶⁻¹⁹ These scores have been suggested to select patients for an intensified treatment, and rely on the summation of points associated with clinical factors that are independently predictive of stroke risk (age, blood pressure, clinical manifestations, duration of symptoms and diabetes).^{20,21} The ABCD3-I includes imaging and dual TIAs within seven days in addition to the ABCD2-score.

Another risk score, Carotid Artery Risk score (CAR), estimates the 5-year ipsilateral stroke rates in a recently symptomatic patient with carotid stenosis of 50% or more treated with a modern optimized medical therapy (OMT). This scoring system has not been validated and is therefore regarded as provisional until the ECST-2 study has been completed. The CAR score includes age, gender, degree of stenosis, time from event to treatment, most severe ipsilateral event, previous myocardial infarction (MI), peripheral vascular disease, diabetes, hypertension and whether the plaque is ulcerated or not.

Treatment of symptomatic carotid stenosis

There are two important strategies for treating patients with symptomatic carotid stenosis, medically and surgically. The most important is probably the medical treatment, which has changed considerably over the past decades.

Medical treatment

Patients with symptomatic carotid stenosis should be informed about risk factor control. They should be advised stop smoking and offered smoking

cessation interventions. Exercise and avoiding obesity should be advised. In a meta-analysis, moderate or high levels of physical activity were associated with 25% relative risk reduction in ischemic stroke.²² Further, obesity is shown to increase risk of stroke prevalence, RRI 1.64 (95% CI 1.36 – 1.99).²³

Antihypertensive treatment is recommended for patients with hypertension and asymptomatic extracranial carotid disease, to maintain a blood pressure below 140/90mmHg.^{24,25} In recently symptomatic patients with severe bilateral stenosis, aggressive antihypertensive treatment may not be advisable. However, a systolic blood pressure >180mmHg is an independent predictor for stroke after CEA. The recommendation is to reduce the blood pressure <180mmHg before surgical treatment. The evidence of benefit of a specific target blood pressure has not been established in the relation to the risk of exacerbating cerebral ischemia.^{26,27}

Treatment with statin is recommended prior to intervention in all patients undergoing CEA to reduce 30-day incidence of death and stroke.²⁸⁻³⁰ Merwick et al showed a reduction of stroke in patients with acute symptomatic carotid stenosis treated with statins.³¹

Regarding antithrombotic therapy, antiplatelet is recommended before oral anticoagulant as first choice treatment of extracranial carotid disease for prevention of cardio- and cerebro-vascular events. Aspirin alone or combinations with dipyridole, or clopidogrel alone are the first choice treatment in AHA guidelines.³²⁻³⁷ Several studies have shown a benefit with dual antiplatelets (DAPT), aspirin and clopidogrel to prevent recurrent stroke in symptomatic carotid stenosis awaiting revascularization.^{21,35,38,39}

Batchelder et al showed a significant reduction in recurrent neurological events and spontaneous embolization prior to CEA without a significant increase in perioperative bleeding complications.⁴⁰ However, there is a reason for caution since some studies shows a higher risk of hemorrhage performing CEA with dual antiplatelet therapy.⁴¹

Surgical treatment

In a meta-analysis, including more than 6000 patients, randomized within ECST, NASCET and VA the benefit of intervention within 14 days (from most recent event to randomization) was shown.^{42,43} Carotid revascularization in symptomatic carotid stenosis is, after these results, recommended in patients at low or average surgical risk who has had a non-disabling ischemic stroke, transient ischemic cerebral event with hemispheric symptoms or ocular TIA within the last 6 months.^{37,44} The perioperative stroke and/or mortality risk should not exceed 6%.^{42,43}

There are several techniques for carotid revascularization. The two standard interventions are carotid endarterectomy (CEA) and carotid artery stenting (CAS). There are no studies showing the advantage for CAS in the acute period of symptomatic carotid disease, and therefore CAS will not be discussed in this thesis. CEA can be performed as a conventional endarterectomy or eversion endarterectomy.

There are different advantages and disadvantages with both methods. No randomized trials comparing the two techniques have shown any differences in morbidity or mortality, or rates of restenosis.^{45,46}

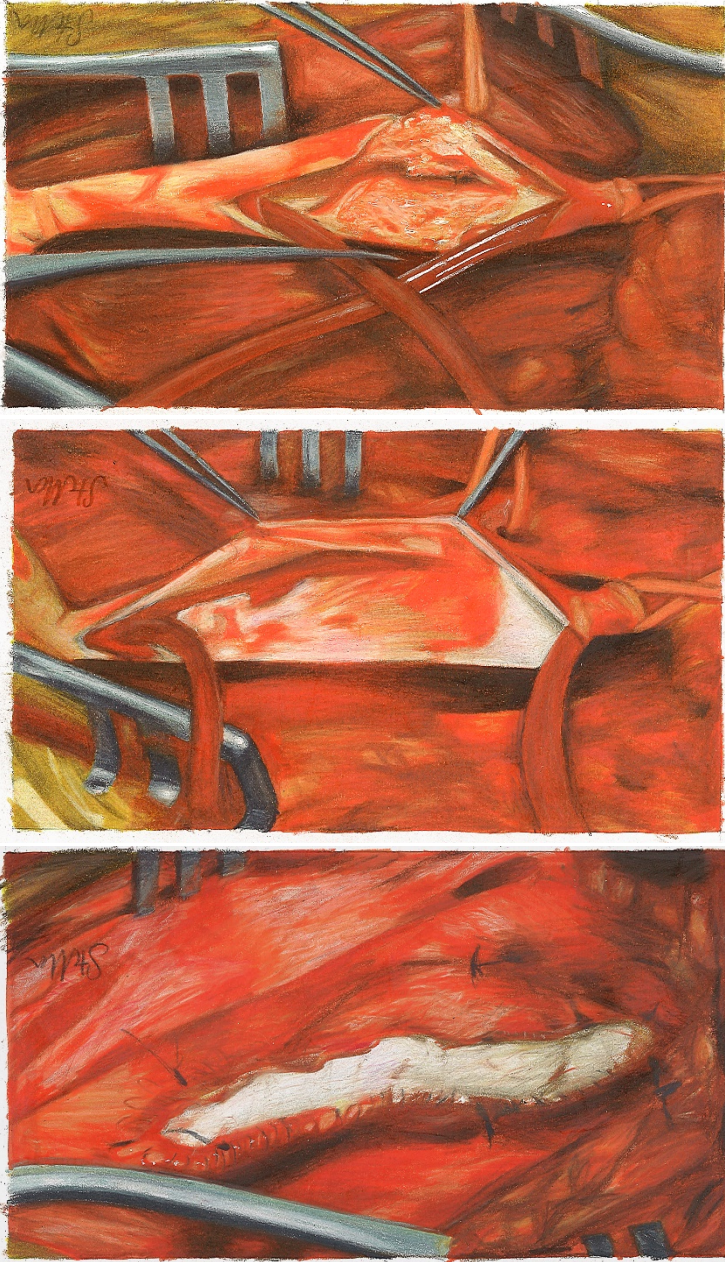


Figure 2. Carotid endarterectomy with use of shunt and patch.

Timing of carotid endarterectomy

The optimal timing for CEA after TIA or stroke remains an important and controversial issue. The risk of recurrent stroke should be balanced to the procedural risk. Most guidelines recommend that CEA should be performed within 14 days of symptom onset.^{37,44,47}

In the UK, the National strategy for stroke has adopted an even more aggressive approach and has recommended that symptomatic patients should undergo CEA within 48h of symptom onset.⁴⁸ There is relatively little evidence supporting the 48h threshold in literature.

Definitions in literature

The different definitions of the neurological recurrent events (first event, index event, alarm symptom, referral event) complicate comparison, when trying to summarize the results from studies. The definition of a recurrent event based on first neurological event will overestimate the risk of recurrence then there is a population with “first neurological event” that never will be known to the health care system.

Different studies are answering different questions. There is a disparity between studies that analyze the risk of recurrent stroke in patients not eligible for CEA and/or before known to the healthcare system, and studies that analyze the risk awaiting revascularization and/or recurrent stroke after the index event. Some studies also summarize the total risk of neurological recurrence, TIAs and stroke altogether.

Regarding procedural risk, most studies present the results as risk of CEA stratified from most recent event. These results must be identified separately from the procedural risk stratified from the index event, which would possibly yield a different outcome.

Risk of recurrent stroke

There is definite evidence that the highest risk period for stroke, after suffering a transient ischemic attack, is the first two weeks, and especially the first few days. Natural history studies of neurological recurrence have been reported but with changing of medical treatment regimen the past decades the risk of recurrence is presumably altered as well.⁴⁹

It is important to evaluate the risk in relation to best medical treatment given and also the individual risk for each patient. Contemporary natural history studies report that the incidence of recurrent ischemic stroke after an index TIA ranges from 2 to 8% at 48 hours, 4 to 17% at 72 hours, 8 to 22% at 7 days and 11 to 25% at 14 days.⁵⁰⁻⁵³ Studies with highest risk of recurrent stroke includes stroke in evolution (SIE), probably not caused by a new embolization.

Procedural risk

The early high risk of recurrent stroke led to the recommendations to intervene early. Acute best medical treatment and CEA within 14 days of index event was recommended in most guidelines last decade.⁴² Data suggested that the procedural risk changed dependent on the timing of CEA with highest risk close to the index event.

There were no studies on the peri-operative risk in the hyperacute time period after index event (0 to 2 days) and, today, there are still few studies reporting risk after CEA, stratified for delay, and only a minority of the patients in the studies underwent CEA within 48 hours.

Different results partly due to different definitions of index event are presented. Most studies shows the risk of CEA in relation to time from most recent event and other studies presents the perioperative risk in relation to index event (defined as the event that led the patient to medical attention). Existing studies show that CEA could be performed day 3 to 14 with a low procedural risk, but there is very limited information on procedural risk day 0 to 2.⁵⁴⁻⁵⁶

Changes over time

The three landmark RCTs regarding carotid endarterectomy (NASCET, ECST and VA) have been a great source of knowledge, and have been used in several sub-analysis over time.^{9,10,57} However, there are some problems associated with use of data from populations randomized more than 20 years ago. The study design in these three trials are similar, but there are some differences in methodology.

Veterans Affairs included only men, and the time after last neurological event to randomization had to be less than four months. In NASCET and ECST both genders were included and the elapsed time from last event to randomization had to be less than six months. Surgery, if assigned, should be performed at the earliest opportunity after randomization. The median time from randomization to trial surgery was 6 days.⁴³

The best medical treatment at time of inclusion was, 1300mg/day aspirin in NASCET, 325mg/day in VA, and was unspecified in ECST.

Uncertainty, when studying procedural risk stratified for delay and optimal timing of surgical treatment with those data are obvious. The pooled data from the landmark RCTs, are analyzing procedural risk stratified for delay from most recent event to randomization and not from index event to CEA.⁴³

Furthermore, the advances in medical treatment the last decade raise the issue if the results from older studies are relevant today.

Aims

The overall aim of this thesis was to investigate optimal timing of surgical treatment in patients with symptomatic carotid stenosis.

Specific aims;

To assess the early risk of recurrent stroke in symptomatic carotid artery stenosis (study II).

To evaluate the procedural risk in symptomatic carotid stenosis when CEA is performed within two days from the index event (study I, III and IV).

To evaluate if other procedural risk factors explain or contribute to the observed increase in risk when performing urgent CEA (study I, III, IV).

To evaluate changes over time in risk of recurrent stroke and procedural risk.

Patients and Methods

Study Design

The study design of the four papers is summarized in Table 1. There are three register based studies and one study with consecutive patients from the region. Study I, III and IV are analyzing the procedural risk and study II is studying the risk of recurrent stroke in patients with symptomatic carotid stenosis.

Table 1. Study design of the four studies in the thesis.

	Design	Patients	Source	Primary endpoint
Study I	Prospective national cohort study	n 2596	Swedvasc	30-days Stroke/Death after CEA
Study II	Retrospective cohort study	n 397	WINGA	30-days Stroke/Death in SCS-patients
Study III	Prospective controlled study	n 418	Consecutive regional hospital data	30-days Stroke/Death after CEA
Study IV	Matched cohort study Prospective national cohort study	n 561 n 4978	Medical records and Swedvasc	30-days Stroke/Death after CEA

*SCS=symptomatic Carotid Stenosis

Swedvasc (Study I and IV)

The Swedish registry for vascular surgery was created in 1987, and was nationwide by 1994. All centers performing carotid endarterectomy are registering in the web-based registry. Preoperative data as co-morbidities and demographics are recorded along with procedural data. Thirty day follow-up data includes morbidity, complications and outcome. In May 2008 an updated version of the registry was launched, including alarm symptom, most recent event and time to intervention.

The registry is linked to the Swedish National Population Registry, and the mortality data is therefore 100% accurate. External validation of the Swedvasc registry was performed 2000-2004 with an external validity regarding the carotid procedures of 93.4%.⁵⁸ An even more recent validation of the carotid procedures, 2012, showed an external validity of 98.8%. The internal validity in this study was estimated to 97.4%.⁵⁹

WINGA (Study II)

“Western region INitiative to Gather information on Atherosclerosis” is a registry, which hold information on the clinical results of all carotid ultrasound examinations performed at Sahlgrenska University Hospital from January, 2004 until 2012. Sahlgrenska University Hospital is the sole supplier of vascular ultrasound diagnostics in the Gothenburg region with approximately 650,000 inhabitants.

Ultrasound is the recommended first line investigation of carotid arteries after TIA and minor stroke according to strict local guidelines. The registry thus included all patients in this geographical area, who were referred for evaluation of carotid atherosclerotic disease.

Definitions

In study I, III and IV we used the definitions from Swedvasc;

Alarm symptom / Index event / Referring event and Qualifying event: is the neurological ischemic symptom that brought the patient to hospital, except in paper III, there qualifying event is defined as most recent event.

Most recent event: is defined as last ischemic symptom preceding CEA.

Diabetes Mellitus: is defined as diabetes treated with oral antidiabetics and / or insulin.

Hypertension: if on antihypertensive medication.

Heart risk: is answered with yes if patient suffers heart failure, angina pectoris, earlier MI.

Amaurosis fugax / ocular TIA / ocular stroke: cannot be differentiated and is registered as the same type of index event.

TIA: neurological deficit lasting < 24 hours.

Crescendo TIA: daily ischemic events immediately before CEA, including progressive stroke and stroke in evolution.

Minor stroke: is defined as neurological symptoms lasting more than 24 hours, but less than one week, or minor disabilities.

Major stroke: major disabilities lasting more than 24 hours.

Stroke in evolution: continuously worsening or fluctuating symptoms (included in crescendo TIA in Swedvasc).

Stroke within 30 days is registered as minor or major stroke and categorized as ipsilateral, contralateral, hemorrhagic, ischemic and/or vertebrobasilaris-territory.

In study IV, the definitions crude and validated Swedvasc data are used. Crude Swedvasc data are data that are collected from the registry without cross-checking in medical records. All data referred as validated data are brought from medical records at the local hospital.

Ethical approval

The Gothenburg Regional Ethical Review Board approved the protocols. In Study III, written informed consent was obtained from all participants. In all other studies registry data was used as approved by the Ethical review board.

Patients and primary endpoints

Study I

Hypothesis: There is no increased procedural risk of CEA for symptomatic carotid stenosis in relation to time from index event. - studied in a national population-based registry cohort.

Data for patients who underwent intervention for symptomatic carotid stenosis in Sweden, between May 12, 2008, and May 31, 2011, were obtained from Swedvasc. Patients registered as receiving stenting, ligature, bypass, exploration or transposition were excluded. Three patients were excluded due to missing follow up at 30 days.

All data regarding co-morbidities, demographics, procedural risk and time from index event to CEA were collected from the registry. Procedural adverse events were defined as minor stroke, major stroke or death.

The study population (n=2596) was divided into four subgroups depending on time to intervention: 0 to 2 days (n=148), 3 to 7 days (n=804), 8 to 14 days (n=677) and 15 to 180 days (n=967). Complication rate was then stratified for all four subgroups.

The primary endpoint was stroke and/or death within 30 days of CEA. A multivariable analysis was also performed to identify independent risk factors for CEA.

Study II

Hypothesis: The early risk of recurrent stroke in patients with symptomatic carotid stenosis is as high as earlier studies have described.

All patients with carotid examination, 2004 to 2006 and 2010 to 2012, from the WINGA registry were collected. Patients in the registry with significant carotid stenosis, defined as NASCET $\geq 50\%$, were analyzed. The medical record of each patient was searched manually.

Patients with symptomatic carotid stenosis $\geq 50\%$ (NASCET) were included, while patients with lower grade stenosis, asymptomatic stenosis or occlusion were excluded. Major stroke and stroke-in evolution (SIE) as index event were exclusion criteria. Time and type of index event, time to ultrasound from referral event and time to CEA or primary endpoint were monitored. The patients were censored at time of CEA, recurrent stroke/death or 30-days follow-up.

Primary endpoint was recurrent stroke, defined as ipsilateral ischemic event lasting more than 24 hours or being fatal. Patients with minor stroke as index event were considering having a recurrent stroke if clinical worsening of symptoms were clearly described. NIHSS-score was available from 2010. In the cohort 2004 to 2006 the worsening of symptoms was approximated before and after recurrent event through the medical records (differs from the description in published paper, errata is

sent to the editor of EJVES). Recurrent TIAs were not included as endpoint.

Two different cohorts depending on referral time were chosen, 2004 to 2006 and 2010 to 2012. The purpose was to analyze two cohorts with different clinical properties. In the earlier cohort there was longer delay between referral event, ultrasound and CEA, having the opportunity to longer follow-up but missing some patients with major strokes before ultrasound has been performed.

The later cohort, 2010 to 2012, has the advantage that ultrasound investigation was performed with short delay from referral event, but the follow-up time was limited due to a shorter delay to CEA. The medical treatment was also a factor that had changed in between the two periods, and could be important for the results.

Study III

Hypothesis: CEA within 48 hours would not increase, or only slightly increase, the risk of per- or postoperative complications versus CEA performed during the later period (day 2 to 14).

The Carotid Alarm Study, was a population-based, prospective study of consecutive patients undergoing CEA within 14 days of symptomatic carotid stenosis. Patients were included from October, 2010 to December, 2015 at two centers in the region. Procedural risk was analyzed in patients having CEA within 48 hours and compared with those operated on between 48 hours and 14 days after an ipsilateral ischemic event. Patients with major stroke, NIHSS >5 or infarction >3cm on diffusion weighted magnetic resonance imaging (MRI) were excluded, as well as patients with SIE, severe life-limiting disease and intravenous thrombolysis due to the ischemic event.

The primary endpoint was the composite of death and/or any stroke within 30 days of CEA. Secondary outcomes were any stroke, ipsilateral stroke or ischemic ipsilateral stroke within 30 days of surgery.

Study IV

Hypothesis: There is no increased procedural risk of CEA for symptomatic carotid stenosis in relation to time from index event. - studied in a validated population based cohort.

In study IV, we obtained data on all patients in the register from May 12, 2008 until October 31, 2014 who had carotid endarterectomy (CEA) within two days from alarm symptom (n=343) They were matched 1:1 to a cohort that was registered to have undergone CEA day 3 to 7 from alarm symptom. Two factors, already known to influence timing of CEA, were used for matching, type of index event and which part of the week the patient was presented to health care.

Validation of the parameters in the Swedvasc registry was performed using individual's medical records. Due to a high proportion of misclassification the matching was abandoned and all patients with validated data and CEA within 7 days from index event were used in further analysis. Procedural risk stratified for delay was analyzed. The patients were also split into two cohorts depending on which year CEA was performed, 2008-2011 and 2012-2014, to investigate the change over time.

We also obtained data for all patients who underwent intervention for symptomatic carotid stenosis in Sweden between May 12, 2008 and October 31, 2014, and were reported in SWEDVASC (n=4978). Analysis regarding time from index event to CEA and procedural risk was made. The patients were subdivided as in earlier study, 0-2 days (n=352), 3-7 days (n=1906), 8-14 days (n=1302) and 15-180 days (n=1418). We also split the patients into two groups regarding which time period they were treated, (2008-2011, n=3086) and (2012-2014, n=1892). A multivariate

analysis investigating the peri-operative risk per day 0, 1 and 2 separately, with day 3 as reference, was made.

Primary endpoints in both part I and II of the study were all cause mortality and stroke within 30 days of surgery.

Statistical methods

Statistical analyses were performed using the IBM SPSS version 18.0-23.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 test significance analysis or when appropriate in smaller numbers two-sided Fisher exact test. Continuous variables were compared using analysis of variance and expressed as mean with standard deviation. Odds ratio (OR) has been used to compare two groups and expressed as OR with 95% confidence interval and p value.

In Study II the SAS system version 9 was used for Kaplan-Meier curves. Analysis with log-rank test was performed. Confidence intervals were expressed, as was number of patients at risk by different time points, to clearly show censored cases.

In study III, odds ratios and 95% confidence intervals (CI) for the primary and secondary endpoints were calculated using logistic regression analysis. For the primary endpoint, variables with a p value < 0.1 in the univariate analyses were included in a multivariate model.

In study I, III and IV, multivariate associations were assessed by a logistic regression analysis and results are presented as ORs with confidence intervals (95%). Significance was assumed as $p < 0.05$.

Results

Summarized results

The results from all four studies in this thesis are summarized in Table 2. These results indicate an increased procedural risk with urgent CEA, which seems to outweigh the risk of early recurrent stroke in patients with symptomatic carotid stenosis. Comparing the results regarding recurrent stroke with procedural risk when 48 hours from index event have elapsed, CEA is favorable compared to non-surgical management.

There are several limitations with this comparison. Some patients are included in more than one of the studies, and some of the results in the table are extracted from the study results even though it was not the primary endpoint.

Study I

The overall stroke and mortality rate in 2596 Swedvasc-registered CEAs performed between May, 2008 and May, 2011, was 4.8%. There was no significant increased risk if CEA was performed within 14 days compared to surgery two weeks after the index event (4.5% vs 5.4%).

When the population was subdivided according to time to intervention from index event the stroke/death risk of urgent CEA, within 2 days, was significantly higher, 11.5% (Fig 3). Only 5.7% (148/2596) of the population had undergone surgery within 2 days from the index event.

In order to investigate if a fast track strategy applied in some vascular surgery units was associated with different surgical risk, five centers with a very high percentage of urgent CEAs were identified. The mortality and stroke rate for CEA performed within 2 days, at these centers, did not differ

Table 2. Summarized results from the studies in the thesis regarding risk of recurrent stroke and procedural risk.

	Pts n	Risk of very early recurrent stroke ¹	Mortality and stroke after urgent CEA ²	Risk of recurrent stroke < 7 days	Mortality and stroke after CEA day 3 to 7	Risk of recurrent stroke <14 days	Mortality and stroke after CEA day 3 to 14
Study I	2596	NA	11.5%	NA	3.6%	NA	3.8%
Study II	397	2.0%	NA	4.0%	NA	4.5%	NA
Study III	418	1.7%	10.9%	NA	NA	3.1%	3.0%
Study IV - validated	4978	NA	7.7%	NA	2.9%	NA	3.0%
Study IV - crude data	561	NA	7.3%	NA	5.8% ³	NA	NA

¹In study II, the incidence of recurrent stroke at day 2, and in study III, recurrent stroke within 48 hours. ²In study I urgent CEA is defined as surgery day 0 to 2 from the index event, in study III, it is defined as surgery within 48 hours and in study IV, the procedural risk in this table presents complication rate when CEA is performed day 0 to 2 from the index event (as in study I). ³Accumulated proportion of crescendo TIA as index event in study IV-validated data compared to study I and IV-crude data.

compared to centers with longer time between index event and intervention (11.3% vs 11.6%).

In a multivariate analysis female gender, diabetes, use of shunt and urgent CEA were considered independent predictors of increased risk. Urgent CEA had OR 4.24 (95% CI 2.1 – 8.7, $p<0.001$) for peri-operative complications compared to patients in the reference group who had surgery day three to seven.

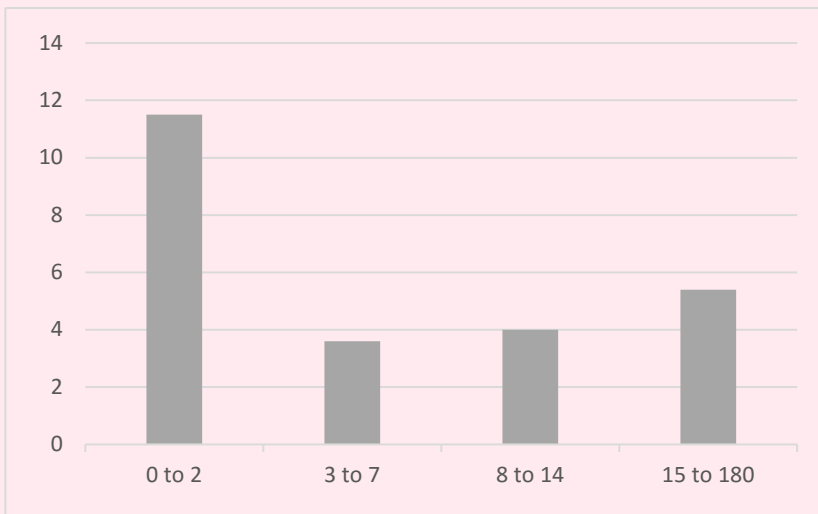


Figure 3. Risk of 30-day stroke/death after CEA depending on time to intervention. Risk is in per cent and time is presented in days from index event. Data from Study I.

Study II

The risk of recurrent stroke within 30 days after an index event, was 7.5% (95% CI 4.4 – 10.6), in patients with symptomatic carotid stenosis (n=397). Within two days 2% (95% CI 0.6 – 4.4) of the patients had suffered a recurrent stroke and after one week the risk was 4% (95% CI 2.0 – 5.9). Patients with minor stroke (n=182) as referring event had a significantly increased risk of recurrent stroke compared to patients with TIA (n=145) (Fig 4). No patients with ocular TIA had a recurrent stroke. Comparing the early cohort (2004-2006, n=194) with the latter (2010-2012, n=203) the frequency of recurrent stroke did not differed significantly (2004-2006; 14/194 (7.2%) 2010-2012; 9/203 (4.4%), p 0.235).

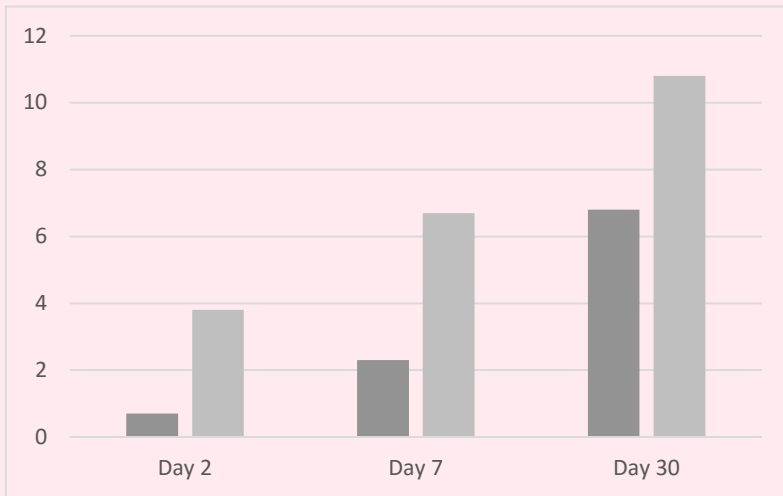


Figure 4. Risk of recurrent stroke at day 2, 7 and 30, from the index event presented in per cent. Dark grey bars presents TIA patients, and light grey bars are patients with minor stroke.

A minor group of patients (n=75) had performed ultrasound within 1 day after index event, with low risk of selection bias. No recurrent strokes had occurred day 2 in this group, however by day seven 4.1% (95% CI 0 – 9.6) had recurred, and by day 30, 9.0% (95% CI 0 – 18.9).

Data regarding medical treatment were missing in many cases due to difficulties in retrieving data from medical records. In the earlier cohort, 147/194 (76%) had data about statins and antiplatelets and in the 2010-2012 cohort data was accessible for 170 of 203 patients (84%). Patients treated with statins when discharged from the hospital, increased from 53% to 97% between these time periods, and at the same time, the use of clopidogrel rose from 4% to 36%.

Study III

A total of 418 consecutive patients were included in the Carotid Alarm Study. The overall 30-day mortality and stroke risk was 3.8%. Out of the 418 patients 75 had CEA within 48 hours from most recent neurological event, and 46 were operated within 48 hours from the referring event. Patients undergoing CEA within 48 hours after most recent event had a significantly increased risk for stroke and/or death as compared to patients undergoing surgery 48 hours to 14 days after qualifying event; 8.0% versus 2.9% (OR 2.90 95% CI 1.02 – 8.23; p 0.049). For the 46 patients who had surgery within 48 hours from referring event the combined mortality and stroke rate was 10.9%.

In a logistic regression analysis use of shunt, CEA performed out of office hours and CEA within 48 hours after qualifying event were all independently associated with a significantly increased risk of stroke and/or death (use of shunt: OR 4.02 95% CI 1.36 – 11.93; p 0.012, CEA out of office hours: OR 3.65 95% CI 1.14 – 11.67; p 0.029, CEA<48 h from most recent event: OR 3.07 95% CI 1.04 – 9.09; p 0.042).

Study IV

Validated Data

In study IV, 686 patients, identified in the Swedvasc registry, were validated through medical records. After validation 561 patients remained for analysis. Twenty-one were excluded due to missing follow-up and 104 patients were misclassified in the Swedvasc registry and had CEA > 7 days after the index event. In this cohort with validated data the overall mortality and stroke rate was 6.4%. Analyzing the procedural risk per day showed a high risk day 0 and 1. Only 57 patients (10%) had surgery within 1 day. When stroke and death rate was compared, between CEA day 0 to 1 and CEA day 2 to 7, there was a significantly increased risk in the group treated urgently (15.8% day 0 to 1 versus 5.4% day 2 to 7, p 0.002, (OR 3.31, 95% CI 1.47 – 7.45)).

The procedure risk in the two time periods 2008-2011 and 2012-2014 were analyzed and showed 8.2% (24/293) risk of stroke/death in the earlier cohort compared to 4.4% (12/268) in the latter cohort (p 0.07). Analysis regarding medical treatment showed a significant increased use of clopidogrel, dual antiplatelet and statins comparing 2008-2011 with 2012-2014 (clopidogrel; 26.6% vs 44.8%, p <0.001, statins; 74.1% vs 86.6%, p <0.001 and dual antiplatelet; 21.5% vs 33.6%, p <0.001).

Crude Swedvasc Data

The overall stroke and mortality rate in the 4978 patients with symptomatic carotid stenosis and CEA from Swedvasc was 3.7%. There was a significant increased procedural risk when CEA was performed day 0 to 2 after the index event (7.7%) compared to day 3 to 7 (2.9%), day 8 to 14 (3.3%) and day 15 to 180 (4.1%). The same analysis as in the validated data comparing day 0 and 1 with 2 to 7, shows significant increased risk with urgent CEA (day 0 to 1; 11.0% (12/109), day 2 to 7; 3.3%

(70/2149), $p < 0.001$, OR 3.4; 95% CI 2.8 – 4.0).

The procedural risk per day, 0 to 3, was analyzed in a multivariate analysis, where day 3 was day of reference. The results showed a 4-fold increased risk for CEA day 0 and 3-fold risk day 1, compared to day 3. In Figure 5, the procedural risk per day (0 to 7) is presented.

Comparing results from the cohort treated 2008-2011 with the cohort treated 2012-2014 showed a reduction in the risk of mortality and stroke after CEA (2008-2011; 4.5% (139/3086) versus 2012-2014; 2.3% (44/1892), $p < 0.001$). Furthermore, in the cohort 2010-2012, only major stroke as complication differed significantly between the urgently treated group (0 to 2 days) and the other groups (3 to 7 days, 8 to 14 days and 15-180 days).

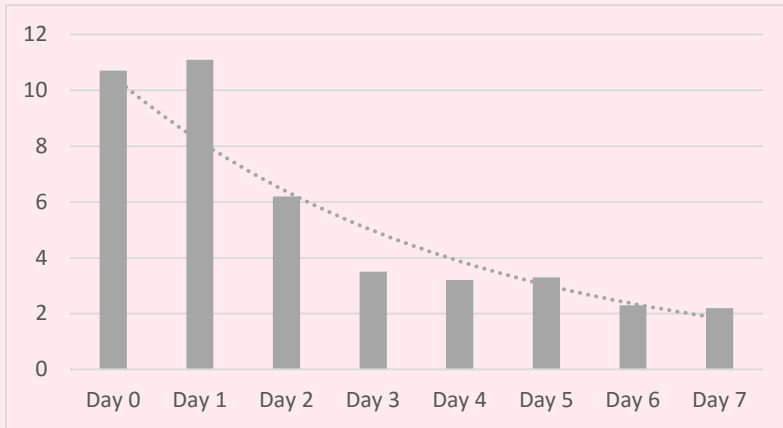


Figure 5. Peri-operative risk exposed in per cent per day, Swedvasc crude data, 2008 to 2014.

Discussion

General discussion

There is convincing evidence that CEA confers maximum benefit if performed within 14 days after the index event. The optimal timing within these 14 days is, however still a controversial issue. The aim of the studies presented in this thesis is to provide further knowledge, in order to determine the optimal timing for surgical treatment.

Natural history of symptomatic carotid stenosis

In study II early risk of recurrent ipsilateral stroke from index event in symptomatic carotid stenosis was shown in a population-based cohort. The risk of recurrent ipsilateral ischemic stroke turned to be lower than earlier studies had shown, 2% by day 2, 4% by day 7 and 7.5% by day 30 (n=397). The early risk of recurrent stroke after an index event is the rationale to perform CEA as soon as possible, and at least within 14 days. The risk of definitive stroke in patients with symptomatic carotid stenosis has to be balanced against the risk of CEA stratified for delay. There is a heterogeneity among studies reporting risk of stroke in patients with symptomatic carotid stenosis. The reasons for these diverse results are manifold, but some of the central definitions that needs to be addressed are;

1. Definition of recurrent stroke. From which event is the recurrent stroke defined? From an event that brought the patient to medical care or from a prior event that the patient never choose to seek medical attention for? Or from a recurrent event that occurred in hospital after admission?

2. Event definition used as inclusion criteria. Which index event constituted the inclusion criterion for each study? Is stroke-in-evolution included? Is ocular TIA included? Are the results reported separately due to type of symptoms at presentation?
3. Timing of inclusion. At what time, in relation to index event, are the patients included?
4. Local tradition. Which medical treatment was considered to be best practice at the time of inclusion? Is this reported separately?
5. Eligibility. Are only patients eligible for CEA included and if so, what is the definition of eligibility for CEA?
6. Censoring at follow up. Studies censored by CEA or CAS will probably show a lower risk of stroke depending on when surgery is performed.

An overview of different criteria used in recent studies are presented in Table 3.

The current guidelines recommend CEA, within 14 days or as soon as possible after the neurological event. Our results are in accordance with those guidelines, even if study II and some more recent studies show a lower risk of recurrent stroke than other studies. In our opinion, the 14 days threshold should be brought forward in order to prevent more strokes in patients with symptomatic carotid stenosis. The medical treatment in the acute period after index event seems to be of major importance for prevention of recurrent stroke in patients awaiting CEA and should be instituted as soon as possible.^{40,60,61}

Ocular TIA, as index event, seems to indicate a lower risk of recurrent stroke compared to TIA and minor stroke.^{38,52,62}

Table 3. Studies regarding early recurrent stroke, different design, definitions and medical treatment.

	Study Design	n	NR from IE or FE (IE/FE)	NR in relation to type of IE is reported (Yes/No)	Patients with SIE are included (Yes/No)	Is BMT reported (Yes/No)	BMT A, C, S	Only patient eligible for CEA is included (Yes/No)	Risk of recurrent stroke <day 2	Risk of recurrent stroke <day 7	Risk of recurrent stroke <day 14
Fairhead (51)	Prospective Population based	85	IE	No	Yes	No	A	No			21%
Bonifati (50)	Retrospective Single center	36	IE	Yes only TIA	No	No	-	No	8%	8%	11%
Shahidi (38)	Prospective Population based	250	IE	Yes	No	Yes	A+C+S	Yes			1.6%
Batchelder (40)	Prospective Consecutive	100	IE	NA	No	Yes	A+C+S	Yes	0%		
Merwick (31)	Prospective Multi center	387	IE	Yes only TIA	No	No	S reported	Yes		8%	
Kashiawasaki (63)	Retrospective Population based	115	IE	No	Yes	No	-	No	2%	4%	7%
Johansson (52)	Prospective Single center	230	IE	Yes	Yes	Yes	A+S	No	5%	8%	11%
Strömberg (62)	Retrospective Population based	397	IE	Yes	No	Yes?	(A or C)+S	Yes	2%	4%	5%
Ois (53)	Prospective Single center	163	IE	Yes	Yes	Yes	(A or C)+S	No	17% (72h)	22%	25%
Marmane (64)	Prospective Single center	36	FE	Yes only Stroke	Yes	No	-	Yes	6%	6%	8%

NR Neurological Recurrent Stroke, IE Index Event, FE First Event, SIE Stroke In Evolution, BMT Best Medical Treatment, NA Not Applicable, A Aspirin, C Clopidogrel, S Statin, CEA Carotid Endarterectomy.

Procedural risk of CEA stratified for delay

Three studies in this thesis have investigated and discussed the risk of very urgent carotid endarterectomy. All three of them (I, III and IV), show similar results with a significant increased procedural risk the first days after index event.

The pooled analysis of NASCET and ECST trials showed a time-dependent benefit of CEA, and the recommendation for revascularization changed from the 4 to 6 weeks delay to a more urgent procedure, within 14 days.⁴² However, this pooled analysis was not designed to address the very early timing of CEA in detail and only stable patients were included. Medical therapy for stroke prevention has improved since these original trials, with an increase in use of statins, more active antihypertensive treatment and a more active antiplatelet regimen. Not only the procedural risk declines with more aggressive medical treatment, but also the risk of recurrent stroke.^{35,38-40,60}

Furthermore, peri-operative stroke as well as stroke in patients awaiting CEA are of similar severity.²⁶ Several studies have reported on procedural risk attributable to early CEA after the pooled analysis of endarterectomy RCTs (NASCET, ECST, VA). There is indisputable evidence that CEA within 14 days from index event is associated with decreased morbidity and mortality compared to medical treatment alone.^{65,66} Within the time frame of two days between index event and CEA there are conflicting results on procedural risk, with small individual studies and lack of standardized definitions for urgent CEA.

DeRango et al concluded that urgent CEA within 2 days from index TIA is relatively safe, with a peri-procedural stroke risk of 2.7%. Stroke as index event was associated with a surgical risk as high as 8%.⁶⁷

There are some larger national audits to report on outcomes, stratified for delays to CEA;

1. Study I in this thesis, reported a significantly increased risk if surgery was performed within 2 days from index event. Only 5.7% of patients were urgently treated (148/2596), but the risk of stroke/death for this small fraction was as high as 11.5% at 30 days.⁶⁸

2. Loftus et al, presented the results from the UK National Vascular registry, in which 3.4% of the cohort (n=780) had CEA within 48 hours, also defined from index event.⁶⁹ The risk for stroke/death was 3.7% in this national audit, which was significantly higher compared to CEA after 48 hours (2.0%, day 3 to 7)

3. An Austrian audit showed that 27% of the patients (206/761) had CEA within 2 days of most recent event.⁵⁴ The stroke/death rate was 4.4% and was not significantly increased compared to CEA after more than two days.

4. A recent German audit, also presented procedural risk within 2 days after most recent event, using the same definition as in the Austrian audit.⁵⁶ The mortality and/or stroke rate was 3.0% with 9.2% of the population having urgent CEA (5198/56279).

5. Study IV (crude data) in this thesis, with partly the same population as in study I, showed that 7.1% of the patients had CEA within 2 days from index event (352/4978), and the procedural risk was 7.7% in this group.

6. In addition, there is also a recent register based study from the Vascular Study Group of New England with 9.7% CEAs performed within 48 hours from index stroke (96/989). This study showed a 7.3% risk of procedural complication in the urgent treated group, which was significantly increased compared to if CEA was performed day 2 to 5 (4.0%).⁷⁰

Notably, the Austrian or German studies have not reported risk stratified for delay after index event. In study IV of the thesis, the daily risk was presented and the procedural risk day zero and one after index event was higher than the thresholds for acceptable risk in guidelines. To summarize the results of these studies, accumulating evidence clearly suggest that the procedural risk the first couple of days are higher than in the later phase.

Studies analyzing the procedural risk stratified for delay from the most recent event do not show any increased risk when performing CEA within 48 hours. The only exception from this is study III in this thesis. A summary of studies analyzing risk of acute CEA is presented in Table 4. The different definitions of urgency as well as outcome are presented. Studies reporting time from the most recent event generally show a lower procedural risk than studies with index event as starting point.

Merging the results from the different groups presented in table 3, the procedural risk of urgent CEA from most recent event is 3.1% versus 4.9% for CEA within 48 hours from the index event.

The procedural risk in patients with ocular TIA as index event is reported low, as is the risk of recurrent stroke for these patients. Furthermore, analysis of the Society for Vascular Surgery Carotid Registry revealed that the risk of perioperative stroke with an index symptom of ocular TIA is no different from that of an asymptomatic patient.⁷¹ Patients with ocular TIA should be recommended the best medical treatment but not surgery, at least if the patient is at high risk factors for surgery.

Table 4. Comparing procedural risk within 48 hours or 2 days from index event or most recent event.

	Patients (n)	Time for CEA from index event/most recent	Stroke/Death n (%)
Barbetta 2014 ⁷²	45	Index event	2 (4.4)
Capoccia 2012 ⁷³	48	Index event	1 (2.1)
Chisci 2015 ⁷⁴	30	Index event	3 (10.0)
Mussa 2009 ⁷⁵	27	Index event	2 (7.4)
Tvisgoulis 2014 ⁷⁶	20	Index event	2 (10.0)
Strömberg 2012 ⁶⁸	148	Index event	17 (11.4)
Strömberg 2015 ⁶²	15	Index event	3 (20.0)
Strömberg (study IV-validated data)	219	Index event	16 (7.3)
Loftus 2016 ⁶⁹	780	Index event	29 (3.7)
Averginos 2017 ⁷⁰	96	Index event	7 (7.3)
Nordanstig 2017 ⁷⁷	75/46	Most recent/Index event	6 (8.0)/ 5 (10.9)
Ferrero 2014 ⁷⁸	176	Most recent	7 (4.0)
Gajin 2013 ⁷⁹	58	Most recent	0 (0.0)
Rantner 2014 ⁵⁴	206	Most recent	9 (4.4)
Sharpe 2013 ⁵⁵	41	Most recent	1 (2.4)
Tsantilas 2016 ⁵⁶	5198	Most recent	156 (3.0)

Optimal timing of CEA

The results from the studies regarding early recurrent stroke and procedural risk lead to the conclusion that CEA should be performed as soon as possible after the index event. However, we consider that surgery within the first 48 hours is an exception to this recommendation and should be avoided due to the increased procedural risk. In our opinion the higher risk of peri-operative complications in day 0-1 outweighs the risk of recurrent stroke in this phase.

There is no evidence of increased procedural risk day 3 to 7 compared to day 8 to 14, it may therefore be wise to consider changing guidelines to a more prompt revascularization strategy aiming at day 3 to 7. It may even be that CEA at day 2 after the index event yields a lower risk for peri-operative complications than risk of recurrent stroke, and maybe this will be the optimal day to aim for.

Considering the results from studies regarding recurrent risk and procedural risk, it is important to note that “high risk” for recurrent stroke is not the same as “high risk” for CEA. A high risk for a recurrent stroke in a patient waiting for surgery does not automatically imply a higher procedural risk. Therefore, the peri-procedural risk has to be carefully balanced to the risk of natural history of the disease.

Changes over time

The risk of recurrent stroke and risk of CEA both changes as optimal medical therapy and life style are changing. In study II, almost two thirds of the patients with recurrent stroke were from the earlier cohort, 2004-2006, but there was no significant difference between the groups. In study IV the results from crude Swedvasc data showed a decreased procedural risk over recent years, comparing 2008-2011 (4.5%) with 2012-2014 (2.3%). There are certainly many factors influencing changes of risk, but medical treatment is the only evident noticeable factor in the studies in this thesis. With an increased use of statins and dual antiplatelets the procedural risk seems to lower as the risk of recurrent stroke awaiting revascularization. Several recent studies support the importance of acute medical strategy.^{21,35,38-40,80}

Methodological considerations – Limitations

Selection Bias

Study I, III and IV includes only symptomatic patients who eventually underwent CEA. Patients deemed to be at high surgical risk, and for other reasons were not offered CEA were not included. In study I and IV, a small percentage of patients undergoing CEA during this time period may not have been registered in Swedvasc. In study I and study IV (crude data) data have been reported wrong in some patients, the reason for doing a validated study from medical records (Study IV- validated data). Vascular surgeons are responsible for reporting 30-days follow-up in half of the cases in Swedvasc, the other part is managed by neurologists. There could be differences between the way neurologists and surgeons report adverse events.

In study II, patients are included at time of ultrasound, missing some patients between referring event and investigation. Also, there is a possible bias due to many censored patients undergoing early CEA in the later time period. In Study III the selection of patients are not random. There is a potential risk that urgent CEA is performed in patients where the neurologist or vascular surgeon believes in the benefit, or vice versa. Another limitation with the Carotid Alarm Study is the low proportion of CEA performed within 48 hours. This could have influenced the results.

Information bias

Information bias could be a limitation in all studies based on registry data. Outcome after CEA that is reported by the vascular surgeon who performed the operation tends to be better than if follow-up is performed by someone without relation to the surgeon.⁸¹

Confounding

In study I, III and IV (validated data) the confounders are presented in table one. The most important confounder in the mentioned studies is probably crescendo TIA as index event. The validated part in study IV is stratified for this confounder. The logistic regression analysis performed in study I, III and IV is an attempt to adjust for confounders.

Power

Most trials on procedural risks of urgent CEA suffers from limited power due to the low number of observations in the first few days after index event. Our studies are no exception and we therefore have limited possibilities to study procedural risks especially within the first 2 days from index event.

Conclusion

Awareness of the procedural risks of urgent CEA was heightened after the publication of Swedvasc data (study I). Even if the message was clear, that CEA beyond two days from index event was not associated with increased procedural risk, other authors have argued that our article may be a further justification for deferring CEA.⁸² In this thesis, the conclusion regarding optimal timing of surgical treatment, is that acute CEA is safe, with the exception for day 0 and 1, and day 2 is uncertain. Patients will benefit from a more expedited strategy and it is time to change guidelines, and recommend CEA within 7 days from index event, with the exception for the first days after index event.

Ocular TIA has a low risk of recurrent stroke and also a low perioperative risk. The benefit of CEA is not clearly evident in these patients, and further studies are needed.

A more frequent use of dual antiplatelet treatment and statins over time may have altered the risk profile for both recurrent stroke and procedural risk. The impact of intense medical therapy on the optimal timing of CEA is unclear. More studies are needed to analyse the natural history of disease and also the risk of urgent CEA with optimal medical treatment.

Future Perspective

There are still several areas of research in patients with symptomatic carotid disease, which can improve treatment and better answer the question who benefits most from surgery.

The best way to study the optimal timing of surgical treatment in patients with symptomatic carotid stenosis is to study the combined risk of recurrent stroke and procedural risk. Inclusion of patients should be done at time of medical attention or at least within 24 hours from index event. Fast track strategy with ultrasound or CT angiography should enable immediate inclusion of patients with carotid stenosis after their index event to avoid selection bias. Randomisation between OMT and CEA day 0 to 1 and OMT and CEA day 3 to 7 should be studied. Power calculation with power 0.80 and significance level $p < 0.05$ and a possibility to identify a 4% difference in risk (10% vs 6%) would require 721 patients in each treatment arm. Approximately 800 CEAs for symptomatic carotid stenosis are registered each year in Swedvasc. If 40% is included nationwide each year, it would take approximately 4 years to meet the goal of inclusion. An international multi-centre study could be a possibility to further increase the inclusion rate.

Today, we expose patients with no benefit at all to surgical risk. Development of more individualized risk factors for recurrent stroke would improve selection of patients for CEA. Imaging based on plaque morphology and plasma biomarkers for stratifying the risk are developing areas in research, however, much work is needed before they can be used in everyday clinic.

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